SUMMARY MINUTES

OF THE

OPHTHALMIC DEVICES PANEL MEETING

NINETY-FIFTHMEETING

JULY 22-23, 1999

OPEN SESSION

Gaithersburg Hilton
620'Perry Parkway
Gaithersburg, Maryland

OPHTHALMIC DEVICES PANEL MEETING

July 22-23, 1999

PANEL PARTICIPANTS

James P. McCulley, M.D.	Chair
Mark A. Bullimore, MCOptom, Ph.D.	Voting Member*
Eve J. Higginbotham, M.D.	Voting Member
Janice Jurkus, O.D.	Voting Member
Marian S. Macsai, M.D.	Voting Member* *
Jose S. Pulido, M.D.	Voting Member
Joel Sugar, M.D.	Voting Member* * *
Frederick Ferris, M.D.	Consultant, deputized to vote
Michael R. Grimmett, M.D.	Consultant, deputized to vote**+
Alice Y. Matoba, M.D.	Consultant, deputized to vote***
Mark J. Mannis, M.D., F.A.C.S.	Consultant, deputized to vote, ***
Woodford S. Van Meter, M.D.	Consultant, deputized to vote*
Ming Xu Wang, M.D., Ph.D.	Consultant, deputized to vote* * * *
Lynn Morris	Consumer Representative
Marcia S. Yaross, Ph.D.	Industry Representative

*	Primary Reviewer for PMA 990010
**	Primary Reviewer for PMA 98005 1
***	Primary Reviewer for PMA 990014
****	Primary Reviewer for PMA 930034/S 13
+	Non-participant in PMAs P990019 and P930034/S13

FOOD AND DRUG ADMINISTRATION PARTICIPANTS

Sara M. Thornton	Panel Executive Secretary
A. Ralph Rosenthal, M.D.	Director Division of Ophthalmic Devices
James F. Saviola	Chief Vitreoretinal and Extraocular Devices Branch
Morris Waxler, Ph.D.	Chief Diagnostic and Surgical Devices Branch
Ashley A. Boulware	Acting Chief Intraocular and Corneal Implants Branch
Jan C. Callaway	Microbiologist Diagnostic and Surgical Devices Branch Team Leader for PMAs P990010 and P930034/S13
Bernard P. Lepri, O.D., M.S., M.Ed.	Optometrist Vitreoretinal and Extraocular Devices Branch
Everette T. Beers, Ph.D.	Biomedical Engineer Diagnostic and Surgical Devices Branch
Malvina B. Eydelman, M.D.	Medical Officer Division of Ophthalmic Devices
Susanna W. Jones	Toxicologist Intraocular and Corneal Implants Branch Team Leader for PMA P9900 14
Sheryl L. Berman, M.D.	Medical Officer Division of Ophthalmic Devices Clinical Reviewer for PMA P990014

OPEN SESSION-JULY 22, 1999

CALL TO ORDER

Dr. James P. McCulley, Panel Chair, called the meeting to order at 8: 15 p.m. **Ms. Sara M. Thornton, Executive Secretary,** announced a tentative September 23, 1999 panel meeting date and asked panel members to introduce themselves. Ms. Thornton read the conflict of interest statement, noting that a waiver allowing participation had been granted to Dr. Wang and that matters declared by Drs. Bullimore, Ferris, Mannis, Wang, Jurkus, Macsai, and Grimmett had been considered but their full participation was allowed. She also read appointments to temporary voting status for those listed on the panel roster as consultants deputized to vote.

OPEN PUBLIC HEARING

Dr. McCulley invited members of the public who wished to address the panel to speak.

Dr. Karl G. Stonecipher, who had submitted data both for the Summit and VISX laser arms in the CRS trial, spoke in favor of the trial's data collection and clinical monitoring and stated that the CRS LASIK study had been conducted as a true clinical treatment trial. He urged that laser labeling be brought in line with lasers' actual and intended use.

Dr. Peter N. Arrowsmith, a board-certified ophthalmologist, also spoke in favor of the CRS study, saying that it was of excellent quality and had demonstrated that LASIK performed as prescribed upon eyes of qualified patients and using specified lasers and equipment is a safe and effective refractive procedure.

Dr. Keith Liang also spoke in favor of the CRS study, stating that it empowered physicians to regain some autonomy in the direction of refractive surgery, enabled them to study a procedure they thought best for their patients, and allowed for efficient enrollment of patients in a timely fashion. He stated that the panel's expedited review of CRS data and possible approval would signal to physicians that they can contribute to the current healthcare system and that their continued innovations will benefit both their surgical specialty and their patients.

Mr. Ron Link, a representative of an association of patients whose eyes have been damaged by various refractive procedures, urged the panel to work with industry and the medical community on post-surgical refractive problems, saying the standard of care must be raised through new modalities to improve surgical outcomes. He also urged better preoperative criteria for surgery such as pupil size and preexisting conditions and recommended a fund for a study of refractive surgery outcomes to amass a database of agreed-upon complications.

Mitch Barrow, a LASIK consumer, also urged the panel to consider complications such as starbursts, haloes, and ghosting. He recommended an expansion of preoperative and postoperative parameters to include contrast sensitivity, glare, and third-party independent assessments. He also stated that FDA approval should include a range of pupil sizes and that public information should include labeling restrictions.

OPEN COMMITTEE DISCUSSION

Dr. A. Ralph Rosenthal, director of the Division of Ophthalmic Devices, gave the division update, in which he introduced four new division members. He noted that the division

had been enlarged by the addition of the Ear, Nose, and Throat Branch, which might necessitate renaming the division.

Dr. Rosenthal also updated the panel on the FDA's Bioresearch Monitoring Program (BIMO), an agency-wide program to ensure the quality and integrity of data submitted in support of investigation device exemptions (IDEs), premarket approval applications (PMAs), and 5 1 O(k)s and to ensure that human subjects participating in investigations are protected from undue risk. He listed the six program areas covered by BIMO, which include areas such as data audits and implementation of FDA's Application Integrity Policy.

Dr. Rosenthal also noted complaints received by FDA and panel members about the Sunrise PMA, in particular on issues involving biased data and poor study design and execution. He clarified that these issues were not on the agenda for panel consideration and that the panel's mission is to advise the agency on scientific and clinical issues. Conflict of interest and data integrity issues are thoroughly investigated by the FDA in camera, and results are not discussed with the public or with informants.

PMA P990010

Sponsor Presentation

Dr. J. Charles Casebeer introduced the sponsor presentation for CRS Clinical Research, Inc.'s PMA for the VISX Model C "Star" Laser System for the correction of myopia from -1.00 to -14.00 diopters (D) with or without astigmatism of 0.25 to 6.00 D using Laser in situ Keratomileusis (LASIK). He explained the history and evolution of the CRS LASIK study, which

was a large, multicentered evaluation of the approved Summit and VISX lasers for LASIK within the approved refractive range for myopia but which was later expanded for other indications. Dr. Casebeer discussed investigator enrollment, noting enrollment was open to qualified ophthalmologists to reflect LASIK in general use.

Dr. Guy M. Kezirian discussed study logistics and results. He described data collection and monitoring procedures and listed the inclusion and exclusion criteria and operative parameters* He also explained study restrictions on nomograms, fellow eye treatments, and reoperation/enhancements. The study involved 24 surgeons at 21 centers and a PMA cohort of 723 eyes, all of which were treated prior to June 1, 1998. Data on a remainder cohort of 553 eyes were also included in the safety results because outcome comparison showed no statistical differences from the PMA cohort, although investigator compliance was lower.

Dr. Kezirian presented study results on PMA cohort accountability, demographics, attempted corrections, and preoperative refractive distribution. He listed. safety results in terms of five target endpoints, three of which the study met (percentages of those with loss of more than two lines best spectacle corrected visual acuity or BSCVA or those with BSCVA worse than 20/40 and of those with induced astigmatism of greater than two diopters). The study came close to reaching the remaining two targets (percentages of those with haze associated with loss of > two lines of BSCVA and incidence of adverse events per type). Dr. Kezirian also listed four effectiveness target endpoints relating to stability, noting that the study came close to meeting these targets as well. He concluded that the mean refractive changes after one month were

minimal, that stability was achieved at three months by FDA definition for overall cohort, that stability was achieved by one month for the < -7.00 diopter group and at slightly lower rates for the > -7.00 diopter group, and that stability in spheres and spherocylinders was similar.

Dr. Kezirian discussed nomogram use, noting that the nomogram was based on overall laser profiles but individually adjusted to overall profiles on a case by case basis. These adjustments showed the differences between PRK and LASIK treatment amounts to be significant, with LASIK allowing for more accurate treatments. The adjustments also demonstrated the need for software and individual nomogram adjustments. Dr. Kezirian also discussed patient symptoms as covered in a questionnaire administered preoperatively and at three months postoperatively. Symptomatic questions related to glare and halo showed improved responses after LASIK compared with preoperative levels. He looked at reoperation data and concluded that reoperations were more common with increased spheroequivalent and cylinder correction. He stated that reoperations were effective in reducing refractive error and glare and in improving uncorrected visual acuity (UCVA) and the risk of BSCVA loss was minimal with reoperations.

Dr. Casebeer concluded that the study had satisfied the published FDA safety and efficacy criteria. He found nomogram adjustments necessary and suggested range limitations, but concluded that approval was in the interest of ophthalmology and the public.

FDA Presentation

Dr. Morris Waxler, chief of the Diagnostic and Surgical Devices Branch, and Jan Callaway, team leader for the CRS PMA for the VISX STAR Excimer Laser System, introduced the FDA presentation. Ms. Callaway introduced the primary panel reviewers and the review team members.

Dr. Bernard Lepri, FDA clinical reviewer, described the six-month investigation, which used 11 investigators to study LASIK for myopic correction in patients demonstrating one year of preoperative stability at indicated ranges of myopia and astigmatism. He read five questions for panel review. In discussing these questions, he presented stability data on MRSE for the full cohort at the one to three month interval and the three to six month interval. He also discussed stratifications of preoperative refractive characteristics and effectiveness outcomes by distribution of preoperative spherical and cylindrical errors. He presented a stratified analysis of spherocylindrical corrections. Dr. Lepri presented a stratified summary of MRSE of +1.OO D at three months and a comparison of MRSE at +1.OO D for stratifications of >7 D at three months and at six months. He described the nomogram adjustment, noting that it was unique to this protocol, and read the sponsor-proposed labeling regarding the nomogram.

Panel Reviews

Dr. Mark Mannis gave the first panel review, noting that the procedure was efficacious in achieving predictable stability at six months and in modulating cornea1 problems. He thought the overall data presented two issues with significant labeling implications: the groups should be

divided into less than or equal to -7.00 diopters of myopia and greater than -7.00 diopters of myopia in terms of efficacy and safety parameters achieved and that nomogram issues should be included. He thought the study well designed with a suitable cohort and data that justified approval with labeling corrections. He recommended that the labeling indicate 1) patients with greater than -10.00 diopters of myopia may experience complications, particularly ectasia, 2) discussion of the nomogram issue and 3) accuracy at greater than -7.00 diopters cannot be as clearly guaranteed as at lower ranges.

Dr. Mark Bullimore provided the second panel review. He thought the PMA should be recommended as approvable with labeling conditions on the range of myopia to be treated. His concerns involved accountability, which he saw as variable and mediocre, and thus introducing the potential for bias. He found the efficacy data the strongest part of the proposal, noting that he had issues with the range of approval for the higher myopia and astigmatism ranges. He was concerned about the risk of cornea1 ectasia for those at or over -10.00 diopters and about the potential for long-term changes in refraction, given the lack of follow-up. He also urged the use of a standardized patient questionnaire.

Panel Discussion

In initial panel discussion, panel members were particularly concerned about accountability, with some arguing that 90% accountability and stability established at three months were sufficient to accept the data and others concerned that acceptance of the data would lower the bar for future PMAs to unacceptable levels. The feasibility of various methods of

obtaining additional follow-up data was discussed, as were the public health implications of approving the PMA with lower accountability versus not approving the PMA and saying nothing publicly about potential side effects.

In discussing the FDA questions, the panel was uncertain how to answer whether the clinical data provided sufficient follow-up, with a majority thinking the data insufficient. The panel agreed that with a six-month data set and 90% accountability, the data set would be sufficient. Panel members thought the presentation of refractive outcome stability was adequate, with the qualifications or labeling conditions that stability may be poorer above -7.00 diopters and that stability had not been studied for more than six months.

On the range of myopic and astigmatic corrections, the panel recommended that the indication be revised to suggest a range of up to -12.00 diopters on sphere and -4.00 on cylinder. Tables stratified by one diopter should be included in the labeling. Labeling on the individualized nomogram should be revised to read, “The programmed amount indicates the average correction that can be anticipated, but actual use will probably require individual adjustments of this amount. Tracking of clinical outcomes is recommended.” The panel wished the FDA to be aware of variables such as changes in technique used by the same surgeon and environmental changes. The panel also recommended that the FDA warning on ectasia should be strengthened to state that the posterior 250 microns should not be invaded because of the risk of post-LASIK cornea1 ectasia. The labeling should also modify the exclusion criteria to be consistent with the trial in excluding those with previous surgical procedures. They recommended a statement in the patient brochure

and labeling concerning adverse effect of pupil size on outcome and a caution that visually significant glare, haze, or halo may occur in the higher ranges of correction and giving the percentages on glare and halo occurrence in these ranges.

OPEN PUBLIC HEARING

Dr. Karl Stonecipher asked to address the panel again. He approved the panel conditions listed above but added that ethical guidelines on refractive surgery should also be put into place.

Ron Link also asked to address the panel again. Heexpressed his happiness that the panel was willing to listen and to address the concerns of refractive surgery patients and called for more research on patients with poor outcomes. He thought it an ethical imperative to donate some of the profits from refractive surgery to a fund for such research.

There were no closing comments from the FDA.

The sponsors noted that panel concerns about leaving 250 microns of the posterior cornea intact were included in the PMA. They noted it would be difficult to obtain further follow-up data by calling patients previously lost to follow-up. They thanked the panel.

Ms. Sara Thornton read the panel voting options and instructions. A motion was made and seconded to recommend the PMA as approvable with the following conditions: 1) The range should be limited to -12.00 diopters of sphere and 4.00 diopters of cylinder. 2) The labeling should include safety and efficacy data stratified in one-diopter steps and indicate that poorer outcomes have been achieved at -10.00 diopters and above. Labeling should also show that stability has been poorer for -7.00 diopters and above and not studied or established beyond six

months. 3) Labeling regarding the nomogram should be revised to read, “The programmed amount indicates the average correction that can be anticipated, but actual use will probably require individual adjustments of this amount. Tracking of clinical outcomes is recommended.” 4) Labeling should state that the residual posterior cornea1 stroma of 250 microns should not be invaded by laser or microkeratome. 5) Cautions should be added regarding patients with previous incisional surgery 6) A caution should be added that glare and haloes may be experienced by some patients, especially those with larger or dilated pupils. 7) The labeling should note that approval data were based on 76% accountability at six months or beyond and that accountability data after six months are insufficient to determine long-term safety and effectiveness.

(An amendment was proposed to make the recommendation contingent upon some assessment of those lost to follow-up. The amendment failed. An amendment was proposed to recommend 90% accountability of the PMA cohort be reached at six months. That amendment was withdrawn.)

A motion to recommend the PMA as approvable subject to the seven conditions listed above was made, seconded, and passed by a vote of nine in favor, none opposed, and two abstentions. The majority of the panel stated that, they voted to recommend the PMA as approvable with the conditions added because the data were sufficient to demonstrate safety and efficacy. Dr. Macsai stated that she abstained because of inability to assess true safety and efficacy due to poor accountability, and Dr. Ferris stated that he abstained because he thought the scientific evidence inadequate for approval.

PMA P980051

Sponsor Presentation

Dr. Douglas Koch introduced the PMA for Sunrise Technologies' Hyperion laser thermal keratoplasty LTK System for correction of unilateral or bilateral hyperopia from +0.75 to +2.50 diopters and less than or equal to .75 D of refractive cylinder in patients 40 years of age or older. He gave a historical review of thermal keratoplasty and summarized the differences between the Summit non-simultaneous contact Holmium: YAG laser and the Sunrise non-contact simultaneous holmium: YAG lasers. Dr. Koch discussed the LTK system, treatment technique, and procedure, and showed post-treatment results. He outlined the history of the PMA since the sponsors' first meeting with FDA in June 1998 in which criteria for submission were outlined. He discussed the FDA definition of accountability and presented PMA accountability data. Dr. Koch noted that 656 LTK eyes were treated with the same algorithm, although the first 46 had a different drying technique.

On safety, Dr. Koch discussed FDA criteria and stated that Sunrise LTK met the target criteria set for BSCVA loss of greater than two lines, BSCVA worse than 20/40, and induced cylinder of greater than 2.0 diopters. He discussed the reported adverse events, noting that no laser-related events were reported during the investigation and that the only complication noted at six months or later was a mild foreign-body sensation. He discussed the current status of cases reporting double vision and symptomatic light sensitivity. Dr. Koch presented postoperative

complications for LASIK and Sunrise LTK procedures, saying that no other surgical procedure has such an outstanding safety profile.

Dr. Doyle Stulting presented efficacy results, based on FDA guidance on effectiveness criteria. He explained the change in drying technique used after the first 46 cases, analyzed the earliest cases, and noted that the early cases were under-treated, leading to less early overcorrection but poorer late results. It was determined that it was not statistically valid to pool the early cases with the remaining cohort. Therefore, all efficacy analyses were presented using the consistent 12-month cohort minus the first 50 cases, which equaled some 357 cases. He noted that in terms of UCVA, the primary efficacy variable, the distance UCVA was stable between six and 18 months post-treatment, and that at six, 12, and 18 months the percentage of those with 20/40 or better met or exceeded the FDA target value. Sunrise LTK also met FDA criteria for +/- 1 .O diopter and +/- 0.5 diopter predictability in MRSE.

Dr. Stulting also discussed patient satisfaction, saying that sponsors had called all patients who reported dissatisfaction at six or 12 months post-treatment. He analyzed the current status of patient satisfaction, noting that no patient mentioned visual symptoms such as glare, haloes, difficulty driving at night, or diplopia as a cause of dissatisfaction. Only 4% chose no fellow eye treatment due to first eye outcome.

Dr. Stulting discussed stability of manifest refraction and rate of change in refraction over time. He noted that the data meet FDA criteria at six months regarding change in spherical equivalent and that the 0.3 mean change of stability is within the range of acceptability. He looked

at hyperopic drift after laser refractive procedures and concluded that the magnitude of change appears to be similar regardless of manufacturer and laser type and that the similarity in drift between studies may be in part due to physiologic changes. He concluded that the PMA cohort results surpass or meet all safety, stability, and effectiveness criteria for refractive lasers and that this technology should be available to physicians and patients in the United States as a refractive surgery option.

Dr. Ralph Rosenthal of the FDA noted that there is a guidance document for low to moderate myopia up to -7 diopters that has been in place since October, 1996. There is no such guidance document for hyperopia. In addition, he stated that the data presented by the sponsors and used as comparison data can only be used for general knowledge only. The data has not been vetted by the FDA and the panel can not be allowed to use it as comparison data.

FDA Presentation

Dr. Waxler introduced PMA team leader Dr. Everette Beers, who read the proposed indications and recognized the FDA review team.

Dr. Malvina Eydelman gave the clinical FDA review, noting that this PMA was for the first nonexcimer laser for treatment of hyperopia. She read the proposed indication and analyzed the original, updated, and updated-minus-50-cases cohorts. She presented accountability statistics on original and updated cohorts and stability data in the original 12 and 18 month consistent cohorts. Dr. Eydelman looked at the change of MRSE of less than or equal to 1 .OO diopter and mean rate of change per month in pair-wise sequential visits for the original and updated cohorts.

She also discussed stability in the original cohort's low and moderate hyperopes. Dr. Eydelman presented statistics on accuracy of manifest refraction, undercorrection, MRSE, and UCVA of greater than or equal to 20/40 and stratified these results by degree of hyperopia and cohort. She also looked at cylinder effect on outcomes, noting that cases with an increase in post-treatment cylinder of greater than or equal to 1 .OO D had significantly more pre-treatment hyperopia than those that did not, and post-treatment UCVA was significantly worse in the increased astigmatism group. Dr. Eydelman discussed visual symptoms in the original cohort and the effect of baseline factors such as cornea1 curvature, age, race, and baseline, spherical equivalent on post-treatment outcomes. She listed safety factors such as BSCVA loss of greater than two lines, adverse events, complication, and the lack of endothelial cell density reduction and read the FDA questions to the panel

Panel Reviews

Dr. Marian Macsai presented the first panel review. She defined hyperopia, accommodation, cycloplegia, absolute and total hyperopia, latent hyperopia, manifest hyperopia, and facultative hyperopia, and expressed concern over lack of cycloplegic data. She noted that PMA accountability was 85% at six months and 69% at 12 months in the three data sets of the various cohorts. In general she noted that low hyperopes fared better than moderate hyperopes, with both doing better at six months than at 24 months. Dr. Macsai noted a refractive drift with an increase in the percentage of patients undercorrected by >1 .OO D, a decrease in those with UCVA of greater than or equal to 20/40, and a decrease in the percentage of those with a UCVA of

greater than or equal to 20/20 from six to 24 months. Dr. Macsai also expressed concern over induction of cylinder of greater than or equal to 1 .O diopters of astigmatism. She found it disconcerting that this induced astigmatism appeared to be increasing in time, yet the sponsor states that the astigmatism "tends to resolve with time." She suggested that follow-up of total hyperopia to the 24 month visit would supply data on refraction and induced astigmatism. Further analysis of these data at 24 months is recommended.

Dr. Michael Grimmett provided the second panel review. He discussed the three PMA cohorts, noting that the original cohort has a large drop-off in follow-up and the updated cohort is missing a large percentage of follow-up. He reviewed the updated minus 50 cohort, with particular emphasis on safety issues. These issues included BSCVA loss of greater than two lines, subjective symptoms such as diplopia and photophobia, and treated versus untreated eye symptoms. On effectiveness data concerning stability of the refractive effect, he saw the lack of cycloplegic data as a major study limitation because residual accommodative reserve might have skewed the results. He concluded that refractive instability was indicated by the shifts in astigmatism magnitude and axis, the progressive declines in UCVA and in proportion remaining +/-0.50 or +/-1.0 D from intended, the progressive increase in undercorrections and in mean MRSE, and the continuous refractive shift with time. He recommended that the PMA be found not approvable because it was not effective in producing refractive stability. He recommended that sponsors complete the data collection for the 12, 18, and 24 month intervals, prepare revised analyses for all of the outcome variables, and resubmit a revised PMA to the FDA in the future.

Panel Discussion

In panel discussion, it was noted that there is no precedent in previous panel deliberations because hyperopia is different from myopia. Panel members discussed the development of physiologic hyperopia versus a genuine hyperopic regression with the device and stated that it was hard to recommend the device to patients in the absence of cycloplegic refraction data preoperatively and postoperatively over time and out to 24 months.

In discussing the FDA questions to the panel, the panel members thought that adequate refractive stability had not been demonstrated with this device by six months and that the current follow-up of eyes was insufficient to provide reasonable assurance of safety and effectiveness. They asked for 24-month data on the updated cohort minus the original 50 cases, with, a minimum sample size of 300 to reach 24 months or a target of 90% accountability. The panel found the decrease in MRSE predictability did raise concerns about treatment efficacy, as did the increase in cylinder and axis. The panel asked for more information and updated data on the increases in visual symptoms such as photophobia and double vision. They also found the safety and effectiveness outcomes do not support approval for the range of hyperopia indicated and asked for more data, which should be stratified by diopter as well. The lack of data on retreatment options with other refractive modalities was thought to be a moot issue at this point. On labeling and other issues, panel members asked for a more detailed gender analysis regarding dry eyes and more data with a minimum of two-year follow-up to make decisions on stability. They encouraged

development of a guidance document on hyperopia, saying the guidance on myopia is not appropriate.

OPEN PUBLIC HEARING

Ms. Sara Thornton read a letter from Dr. Edward Yavitz, an investigator from a laser site, who recommended cycloplegic refractions be done and data stratified by 0.5 diopters as well as by age and sex.

There were no FDA comments.

Sponsor representatives reemphasized that the study showed good follow-up with good acuities that maintain themselves for low hyperopes. Dr. Stulting stated that the United States is behind other countries in refractive technologies and that there is a need for this device, which effectively treats low hyperopes and provides a favorable regression profile. He urged the same standard be applied to all PMAs and urged approval of this PMA to get new, safe technologies to the public in a timely fashion.

Ms. Thornton read the panel voting instructions and options. A motion was made and seconded to recommend the PMA as not approvable because the data did not sufficiently demonstrate effectiveness. Issues that should be addressed to put the PMA into approvable form included a need for cycloplegic data at all time intervals, a stratified analysis on the first 46 cases, a stratified analysis on the updated cohort minus the first 46 cases, an updated questionnaire on visual symptoms, a gender analysis of near visual acuity, and 90% accountability or a minimum of 300 patients reaching the 24 month visit. The motion passed unanimously. Panel members

commended the sponsors for their data collection to date, but said more efficacy data were needed on this new technology. Several panel members again stressed the need for a guidance document on hyperopia.

'Panel Chair Dr. McCulley thanked the panel for their work and day's meeting at 6: 10 p.m.

OPEN SESSION-JULY 23, 1999

Panel Chair Dr. James McCulley called the meeting to order at 8:25 a.m. and asked the panel to introduce themselves. **Panel Executive Secretary Sara M. Thornton** read the conflict of interest statement, noting that waivers had been granted to Drs. Van Meter, McCulley, Higginbotham, Wang, and Pulido, allowing their participation, and that full participation of the other panel members had also been allowed. She also read appointments to temporary voting status for those consultants listed on the panel roster,

OPEN PUBLIC HEARING

Dr. William Bond, a Summit CRS investigator, spoke in support of labeling the Summit Apex Plus laser for LASIK, citing it as the true standard of care for refractive surgery. He stated that the laser should be approved and labeled for its most common actual and preferred use. He stated that patients would benefit from labeling the Summit laser for LASIK because it would permit access to the best LASIK software and frank exchange among physicians and manufactures. On-label LASIK would also resolve issues of professional liability insurance by clarifying that it is the established standard of care refractive surgery.

There were no other requests to address the panel.

OPEN COMMITTEE DISCUSSION

Branch Updates

Dr. James F. Saviola; chief of the Vitreoretinal and Extraocular Devices Branch, gave the update for his branch. He discussed modifications made on July 12, 1999, to the list of

recognized standards used in the premarket review process, which included the American National Standards Institute (ANSI) Z.80.20-1998. He noted that the FDA had approved the Bausch & Lomb Purevision soft contact lens for seven-day extended wear by aphakic or non-aphakic patients. He also notified the panel that two companies have now received a marketing clearance for their lens tinting service, Colorsoft Laboratories and Adventures in Colors, which offers a tinting process for lenses already prescribed by a practitioner as well as a prosthetic tinted lens. Other lens tinting services are working with FDA to meet regulatory requirements.

Dr. Everette T. Beers, acting chief of the Diagnostic and Surgical Devices Branch, gave the update for his branch. He recognized a number of members from his and other branches in the Division of Ophthalmic Devices for the continued high quality of their scientific reviews and team leading. Dr. Beers noted that PMA P970001 for the Emory Vision Correction Center's refractive surgery laser for myopia using LASIK remains under review. He added that the guidance document on information submitted in an IDE application for refractive surgery lasers has not been revised beyond the October 10, 1996 edition. Dr. Beers stated that four original PMAs, 24 PMA amendments, and 13 PMA supplements have been submitted by 11 manufacturers. Over the last 12 months, 542 IDEs were received, of which 212 were submitted by manufacturers (6 originals and 206 amendments and supplements) and 330 were submitted by sponsor-investigators (12 originals and 3 18 amendments and supplements.) He said that a total of 96 5 1 O(k)s were submitted, of which almost 19% were for microkeratomes.

Ms. Ashley A. Boulware, Acting Chief of the Intraocular and Cornea1 Implants Branch, gave the branch update. She listed two PMAs approved since the January 1999 panel meeting: P98003 1 for the KeraVision Intacs, approved on April 9, 1999, and P960033 for the STAAR surgical Staarvisc, approved on July 2, 1999. Ms. Boulware noted that the Accountability Analysis for Clinical Studies of Ophthalmic Devices was issued in early May as a draft guidance document on the web and that comments received during the 90-comment period would be considered prior to issuance of final guidance. Draft guidance for intraocular lenses was posted on the FDA web site on July 16. She encouraged panel members, industry representatives, and members of the public to submit comments during the 90-day period following the upcoming release of the Federal Register notice. She noted that changes from the last draft include revisions to the updated grid, which was compiled based on panel recommendations and which she summarized. Ms. Boulware also noted that the comment period on reclassification of keratoprostheses and aqueous shunts for glaucoma from Class III to Class II has now ended. Comments will be addressed when the Final Rule is issued. Final guidance documents for both devices have also been issued and are proposed as special controls.

PMA P990014

Sponsor Presentation

Melissa Walker of Bausch & Lomb Surgical, Inc., introduced the PMA for the Hydroview IOL, a one-piece posterior chamber IOL with a foldable hydrogel optic and PMMA haptics indicated for correction of aphakia in patients 60 years of age or older where a cataractous

lens has been removed by extracapsular extraction. It is intended for placement in the capsular bag. She described the company's background and gave a historical overview of IOL model H60M, which is a composite Hydrogel/PMMA lens. Ms. Walker described the core clinical study of 387 patients and 21 investigators, and a haze substudy initiated at the FDA's request on 100 patients using three lens models.

Dr. George Green described the IOL, which is a posterior chamber, one-piece IOL with a hydrogel optic and PMMA haptics. He explained the material composition, characteristics, and manufacturing process and discussed biocompatibility and power stability results. Dr. Green also discussed the folding method and packaging, noting that the Ultem was used in the core study but the Surefold was validated in a clinical evaluation and its data included in the PMA.

Dr. Douglas Koch described the core study design, which was a single-arm, open label, historically controlled study using BCVA and adverse events as the primary evaluation parameters. Core study accountability complied with FDA requirements, and evaluation parameters met or surpassed FDA guidelines. Dr. Koch discussed incidence of broken haptics and optic tears in the study and in the postmarketing history. He described the posterior capsular haze substudy and its design, noting that BCVA at one year was comparable in all three lens model groups and that haze and capsulotomy rates between the Hydroview and PMMA lenses were not significantly different. Dr. Koch noted that the Hydroview lens can be implanted through a 3.4 to 3.8 mm incision, although investigators were not asked to implant the lens in the smallest possible

incision. He concluded that the lens is safe and effective, with an outstanding acuity and safety profile, and offers a unique alternative in foldable IOL technology.

FDA Presentation

Ms. Ashley Boulware introduced FDA review team leader **Susanna W. Jones.** Ms. Jones introduced the review team and noted that some minor engineering and clinical issues need to be resolved before final approval. She stated that a panel review was necessary because the chemical composition of the optic material is different from all other approved IOL materials and because of safety issues such as optic tears, haptic breakage, intraoperative explants, and claims about incision size.

Dr. Sheryl Berman gave the FDA clinical review, which consisted of reading the questions for panel review.

Panel Reviews

Dr. Woodford Van Meter gave a primary panel review. He stated that he found acceptability satisfactory and efficacy well established. He was not concerned about safety issues seeing the breakage and tear issues as related to learning curve. Surgical complications all resolved satisfactorily and BCVA rates exceeded the Stark grid‘rates. He listed four concerns to be addressed in labeling: data on variability in folders used, need for detailed labeling recommendations on proper handling to prevent breakage.and tears, the need for an intact anterior capsular bag for implantation, and removal of wording on incision size, which he thought unsupported by data.

Dr. Alice Matoba gave the second panel review. She reviewed the study design, accountability, efficacy, and adverse events, noting that overall safety and efficacy were not major problems. She expressed concern over haptic breakage and optic tears and wanted more patients studied with the Surefold system. She recommended that the PMA be found approvable with conditions that additional data be provided on the safety of the Surefold system and labeling changes to reflect concerns on haptic breakage and optic tears.

Panel Discussion

Panel discussion concentrated on incision size issues and labeling of the wording. It was also emphasized that the lens should be rinsed with saline before insertion.

FDA Questions

The majority of the panel, with one exception, thought that the data on haptic breakage, optic tears, and intraoperative device explant demonstrated a reasonable level of safety and asked for no additional data. They recommended that labeling should be revised to state the full range of incision size in the study and the mean wound size plus or minus one or two standard deviations. Labeling should state that incision size was not measured prior to insertion. There was discussion but no agreement about recommending that the FDA consider deleting the reference to chronically medically uncontrollable glaucoma patients and to glaucoma surgery. The panel agreed that the PMA data provide reasonable assurance of safety and efficacy to support approval of the device.

OPEN PUBLIC HEARING

There were no requests to address the panel. The FDA had no closing remarks. Sponsors noted that there were no reports of hydrogel absorption.

Ms. Thornton read the panel voting instructions and options. A motion was made and seconded to recommend the PMA as approvable with the condition that mean wound size be reported in the labeling as 3.9 mm plus or minus 2 standard deviations. The motion passed unanimously. Panel members stated that they voted to recommend the PMA as approvable because of its good demonstration of safety and efficacy, although Dr Higginbotham stated that she would still like the glaucoma restriction removed.

PMA P930034/S13

Sponsor Presentation

Dr. Eric Ankerud introduced the PMA for the SVS Apex Plus Excimer Laser Workstation with emphasis discs for the reduction or elimination of mild to high myopia from 0 to -14.00 diopters with or without astigmatism of -0.50 to -5.00 D using LASIK in patients with documentation of a stable manifest refraction over the past year who are 18 years of age or older.

Dr. Charles Casebeer described the background, history, and evolution of the CRS LASIK study and its administrative structure, which included open enrollment to qualified ophthalmologists with IRB oversight.

Dr. Guy Kezirian discussed study design and results. He noted that inclusion and exclusion criteria followed FDA guidance, and he described operative parameters, fellow eye

treatments, and reoperations/enhancements. He explained nomogram adjustment procedures and described the study, which involved 24 surgeons at 20 centers and 1685 eyes in the overall IDE cohort. Of these, 1014 eyes were in the PMA cohort and 672 in the remainder cohort. Outcome comparison showed no statistical differences between the cohorts other than a lower rate of investigator compliance for the remainder cohort. Data on the remainder cohort was submitted in the safety results.

Dr. Kezirian gave the study results for the PMA cohort. He provided accountability and baseline statistics and discussed attempted corrections for sphere and spherocylinder, giving means for various ranges. He presented data on preoperative sphere and cylinder refraction distribution. Dr. Kezirian gave safety endpoints in terms of target percentages, noting that the device met most of these endpoints. On effectiveness, he listed the endpoints and discussed stability/mean MRSE for spheres and spherocylinders, for all eyes and stratified by degree of myopia. Dr. Kezirian discussed stability of less than one diopter change, UCVA of 20/40 or better at six months, and MRSE of plus or minus 0.50 and 1.00 D at six months for all eyes and stratified by degree of myopia. He also showed effectiveness of cylinder correction using SIRC/IRC as stratified by one diopter.

Dr. Kezirian presented results of reoperations, showing frequency of reoperations as a function of original correction and effects of reoperation on BSCVA, UCVA, and manifest spheroequivalent.

Dr. Daniel Durrie presented results and conclusions, discussing UCVA at six months for all eyes and stratified by degree of myopia. He also presented UCVA results at one day postoperatively. Patient symptoms were evaluated by questionnaire administered preoperatively at three months postoperatively, with an additional 115 case results evaluated at six months postoperatively. He noted that glare, halo, and visual fluctuations improved overall after LASIK. Scattergram results showed that nomogram differences were minimal with the Summit Apex Plus Laser. He concluded that stability was established by three months and confirmed at six months in the less than or equal to seven-diopter range. Stability rates were lower in the greater than seven-diopter range, an outcome that was expected and clinically acceptable. Dr. Durrie concluded that the device met safety and effectiveness targets for UCVA of 20/40, MRSE of plus or minus 0.50 and 1 .OO diopters, loss of greater than two lines BSCVA, induced cylinder of greater than two diopters, BSCVA worse than 20/40, haze associated with 1% loss of greater than two lines of BSCVA, and adverse events by type. He thought the PMA therefore presented reasonable assurance of safety and effectiveness.

FDA Presentation

Dr. Everette Beers introduced team leader Jan Callaway, who introduced the review team.

Dr. Bernard Lepri described the six-month investigation, which involved 13 investigators using LASIK for myopic correction for the indications described. He presented stability data on MRSE at the one to three and three to six month intervals. Dr. Lepri also presented stratifications

of preoperative refractive characteristics and effectiveness outcomes and described the nomogram adjustments as he presented the FDA questions for panel discussion.

Panel Reviews

Dr. Joel Sugar presented the first primary panel review. He thought the stability and predictability results were good, but on accountability found it not appropriate to exclude sites that did poorly on accountability or surgical results. He raised questions on the range of myopia that should be approved and recommended that the patient education booklet should be revised to show results on induced astigmatism and vision fluctuation symptoms. He recommended that the panel find the PMA approvable with the conditions that the upper limits of myopia should be revised, that the patient and physician information booklets should be reworded, and that outcomes at specific ranges be specified in terms of overcorrections.

Dr. Wang presented the second panel review. He listed five concerns: that there were pockets of data outside FDA guidelines, that safety guidelines should be clarified because of an FDA/CRS discrepancy concerning the definition of a two line loss of BSCVA, that the higher ranges have insufficient sample sizes, that the nomogram instructions should include the need for consistent individual surgical technique, and that the issue of the 250 micron guideline on preservation of the stromal bed should be discussed. He concluded that the study was well done and showed adequate safety and efficacy, and he recommended the PMA as approvable with conditions relating to the above concerns.

Panel Discussion and FDA Questions

On follow-up, the panel thought the clinical data sufficient, with the qualification that they were not happy with accountability below FDA guidelines. In the panel's judgment, however, accountability for this PMA was in the acceptable range when all factors were considered.

On stability data, the panel thought the PMA ensures adequate stability, with considerations and concerns expressed about the insufficient numbers at higher ranges of correction. On labeling, the panel recommended approval of the full range of indications up to -14.00 D for sphere and -5.00 D cylinder with a warning in the labeling that there are minimal data on the higher ranges and that available data indicate less favorable outcomes at higher ranges. Stratification of the data should be included. This cautionary language should be included in both patient and physician information.

Factors affecting the nomogram such as variations in individual surgeon technique, laser brand, environmental factors, and patient response should be stated in the labeling. The need for a consistent operating technique should be stressed. The wording should also be revised to read, "The programmed amount indicates the average correction that can be anticipated but actual use will probably require individual adjustment so this amount. Tracking of clinical outcomes is recommended."

The panel recommended a warning that the posterior 250 microns of the cornea1 bed should not be disturbed by laser or microkeratome. There was a brief discussion of standardizing the definition of safety, but FDA representatives assured the panel they were aware of the

concern. It was recommended that detailed outcome data for myopia and astigmatism refraction outcomes and symptomatic outcomes be added to the patient and physician brochures.

OPEN PUBLIC HEARING

Mr. K. Wiecinski, a LASIK patient and former high myope, asked to address the panel. He stressed the need for surgeon expertise and implored the FDA to listen to all data and look at areas of missing data. He urged that manufacturers and patients not be put at a disadvantage, but that labeling should insist on accountability and that scientific tests be developed for starring and halo assessment to improve safety outcomes.

Dr. Sugar of the panel noted that a warning on pupil size should be included in this PMA as has been the previous standard.

There were no closing FDA or sponsor remarks.

Ms. Thornton read the panel voting instructions and options. A motion was made and seconded to recommend the PMA as approvable with the following conditions: 1) Warnings on less predictable outcomes in patients needing higher ranges of correction in cylinder and sphere should be included in the labeling. 2) Nomogram individualization should be specified as noted above. 3) The posterior 250 microns of the cornea1 bed should not be disturbed by laser or microkeratome. 4) Specific outcom data should be included in the patient and physician brochures that contains refractive values as well as subjective symptoms such as glare, haloes, or fluctuations in vision. 5) A warning should be added about possible increases in potential adverse patient symptoms in patients with larger pupil size. 6) The Inclusion/Exclusion Criteria in the

labeling should state that the patients have a preoperative refractive stability off 0.5 Diopters of change in the year prior to surgery.

The motion passed by a vote of nine in favor and one abstention. Dr. Ferris abstained in the interest of consistency and because he thought the follow-up data were missing. All other panel members thought the safety and efficacy data were reasonable. Dr. Higginbotham stressed the need for a more sensitive patient satisfaction questionnaire to improve the ability to pick up future complications.

Ms. Thornton noted that guidance documents on IOLs and on accountability were available for public comment. She and Dr. McCulley thanked the panel and participants. Dr. McCulley adjourned the session at 1:20 p.m.

I certify that I attended the Open Session of the Ophthalmic Devices Advisory Panel Meeting on July 22-23, 1999, and that this summary accurately reflects what transpired.

Sara M. Thornton
Executive Secretary

I approve the minutes of this meeting
as recorded in this summary.

James P. McCulley, M.D.
Chair

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